

## BIARYL COMPOSITIONS AND METHODS FOR MODULATING A KINASE CASCADE

### RELATED APPLICATIONS

[0001] This application is a continuation application of U.S. Ser. No. 16/893,469, filed Jun. 5, 2020, which is a continuation application of U.S. Ser. No. 16/655,309, filed Oct. 17, 2019, which is a continuation application of U.S. Ser. No. 16/295,018, filed Mar. 7, 2019, which is a continuation application of U.S. Ser. No. 15/408,098, filed Jan. 17, 2017, which is a continuation application of U.S. Ser. No. 14/094,027, filed Dec. 2, 2013, now U.S. Pat. No. 9,580,387, which is a continuation application of U.S. Ser. No. 13/540,940, filed Jul. 3, 2012, now U.S. Pat. No. 8,598,169, which is a continuation application of U.S. Ser. No. 13/152,949, filed Jun. 3, 2011, now U.S. Pat. No. 8,236,799, which is a continuation application of U.S. Ser. No. 11/480,174, filed Jun. 29, 2006, now U.S. Pat. No. 7,968,574, which is a continuation-in-part application of U.S. Ser. No. 11/321,419, filed Dec. 28, 2005, now U.S. Pat. No. 7,300,931, which claims priority to U.S. Ser. No. 60/639,834, filed Dec. 28, 2004, U.S. Ser. No. 60/704,551, filed Aug. 1, 2005, and U.S. Ser. No. 60/727,341, filed Oct. 17, 2005.

### BACKGROUND OF THE INVENTION

[0002] Signal transduction is any process by which a cell converts one kind of signal or stimulus into another. Processes referred to as signal transduction often involve a sequence of biochemical reactions inside the cell, which are carried out by enzymes and linked through second messengers. In many transduction processes, an increasing number of enzymes and other molecules become engaged in the events that proceed from the initial stimulus. In such cases the chain of steps is referred to as a “signaling cascade” or a “second messenger pathway” and often results in a small stimulus eliciting a large response. One class of molecules involved in signal transduction is the kinase family of enzymes. The largest group of kinases are protein kinases, which act on and modify the activity of specific proteins. These are used extensively to transmit signals and control complex processes in cells.

[0003] Protein kinases are a large class of enzymes which catalyze the transfer of the  $\gamma$ -phosphate from ATP to the hydroxyl group on the side chain of Ser/Thr or Tyr in proteins and peptides and are intimately involved in the control of various important cell functions, perhaps most notably: signal transduction, differentiation, and proliferation. There are estimated to be about 2,000 distinct protein kinases in the human body, and although each of these phosphorylate particular protein/peptide substrates, they all bind the same second substrate, ATP, in a highly conserved pocket. Protein phosphatases catalyze the transfer of phosphate in the opposite direction.

[0004] A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a tyrosine residue in a protein. Phosphorylation of proteins by kinases is an important mechanism in signal transduction for regulation of enzyme activity. The tyrosine kinases are divided into two groups; those that are cytoplasmic proteins and the transmembrane receptor-linked kinases. In humans, there are 32 cytoplasmic protein tyrosine kinases and 58 receptor-linked protein-tyrosine kinases. The hormones and growth factors that act on cell surface tyrosine kinase-linked receptors are generally

growth-promoting and function to stimulate cell division (e.g., insulin, insulin-like growth factor 1, epidermal growth factor).

[0005] Inhibitors of various known protein kinases or protein phosphatases have a variety of therapeutic applications. One promising potential therapeutic use for protein kinase or protein phosphatase inhibitors is as anti-cancer agents. About 50% of the known oncogene products are protein tyrosine kinases (PTKs) and their kinase activity has been shown to lead to cell transformation.

[0006] The PTKs can be classified into two categories, the membrane receptor PTKs (e.g. growth factor receptor PTKs) and the non-receptor PTKs (e.g. the Src family of proto-oncogene products). There are at least 9 members of the Src family of non-receptor PTK's with pp60<sup>c-src</sup> (hereafter referred to simply as “Src”) being the prototype PTK of the family wherein the approximately 300 amino acid catalytic domains are highly conserved. The hyperactivation of Src has been reported in a number of human cancers, including those of the colon, breast, lung, bladder, and skin, as well as in gastric cancer, hairy cell leukemia, and neuroblastoma. Overstimulated cell proliferation signals from transmembrane receptors (e.g. EGFR and p185HER2/Neu) to the cell interior also appear to pass through Src. Consequently, it has recently been proposed that Src is a universal target for cancer therapy, because hyperactivation (without mutation) is involved in tumor initiation, progression, and metastasis for many important human tumor types.

[0007] Because kinases are involved in the regulation of a wide variety of normal cellular signal transduction pathways (e.g., cell growth, differentiation, survival, adhesion, migration, etc.), kinases are thought to play a role in a variety of diseases and disorders. Thus, modulation of kinase signaling cascades may be an important way to treat or prevent such diseases and disorders.

### SUMMARY OF THE INVENTION

[0008] Compounds of the invention are useful in modulation a component of the kinase signaling cascade. Some compounds may be useful in modulation of more than one component of a kinase signaling cascade. The compounds of the present invention are useful as pharmaceutical agents. The compounds of the invention may be useful for modulating regulation of a kinase which may be involved in a normal cellular signal transduction pathway (e.g., cell growth, differentiation, survival, adhesion, migration, etc.), or a kinase involved in a disease or disorder. Such diseases and disorders include, without limitation, cancers, osteoporosis, cardiovascular disorders, immune system dysfunction, type II diabetes, obesity, and transplant rejection.

[0009] The compounds of the invention are useful in treating diseases and disorders that are modulated by tyrosine kinase inhibition. For example, the compounds of the invention are useful in treating diseases and disorders that are modulated by Src kinase. The compounds of the invention may also be useful in treating diseases and disorders that are modulated by focal adhesion kinase (FAK).

[0010] For example the compounds may be useful as anti-proliferative agents, for treating mammals, such as for treating humans and animals. The compounds may be used without limitation, for example, as anti-cancer, anti-angiogenesis, anti-metastatic, anti-microbial, anti-bacterial, anti-fungal, anti-parasitic and/or anti-viral agents. The compounds of the invention are useful, for example, in treating